

STAMPEDE Case Study: Using a Master Protocol Approach to Improve Outcomes in Prostate Cancer

Prior to the early 2000s, standard of care for high-risk prostate cancer remained relatively stagnant, with no meaningful improvements in outcomes. Long-term hormone therapy controlled tumors for some time, yet this control was only temporary and men with prostate cancer generally continued to see poor outcomes. However, there were some improvements developing through research in late-stage prostate cancer, and a better understanding of the disease was emerging.

In an effort to embrace new opportunities to make forward advancements in the prostate cancer field, a study team decided to undertake STAMPEDE, a multi-arm, multi-stage platform trial. Implementing a master protocol to guide a disease-centered trial enabled the study team to test multiple therapies at the same time, add new comparisons over time, and move swiftly away from therapies that were not showing sufficient promise at interim analyses. Since its launch in October 2005, the STAMPEDE trial has tested 10 research treatments in a seamless Phase II/III approach. Recruitment was ongoing at the start of 2020 with nearly 12,000 patients recruited and approvals in place to test further treatments.

CHALLENGE

Despite little movement in the prostate cancer field for decades prior to the trial, a number of improvements to the standard of care have emerged during the course of the trial, many emerging from STAMPEDE itself. These required the study team to consider how best to implement these changes into the multiple arms of their study.

Standard of care changes included:

- ◆ 2011 – **Radiotherapy** was found to increase survival for non-metastatic patients. (NCIC PR.3/MRC PR07 and SPCG7)
- ◆ 2015 – A new **chemotherapy** agent was shown to have a survival advantage (STAMPEDE, CHAARTED, GETUG-15). This change led to one of the most pivotal decisions the study team faced because of its major impact on an investigative radiotherapy arm. Prior to the standard of care change, patients randomized to the radiotherapy arm received treatment eight weeks after randomization. However, because clinicians on the study team felt it was not safe to administer both radiotherapy and the new chemotherapy agent simultaneously, the team made the decision to administer radiotherapy six months after randomization—meaning that this investigative arm did not differ from the control arm for the first six months
- ◆ 2017 – A novel form of hormone therapy was shown to have a survival advantage (STAMPEDE, LATITUDE). However, the use of this drug was not approved in the U.K., where the majority of the study's patients were enrolled.
- ◆ 2018 – **Radiotherapy** was found to increase survival for men with low-burden metastatic disease. (STAMPEDE, HORRAD)
- ◆ 2019 – Further novel **hormone therapies** show survival improvement, each with high costs.

Deciding whether to update standard of care for ongoing comparisons in STAMPEDE was sometimes difficult. If the study team chose not to update it, future results could be considered less relevant having tested a new treatment option against an outdated control. If they did implement the change in their study, they had to decide the best, most seamless way to do so while considering how to combine the new standard with ongoing investigative treatments. These changes were particularly challenging for the trial team because the ongoing comparisons included in the master protocol were at different stages—including starting recruitment, completing recruitment, or near completing follow-up. Specific considerations surrounding each decision about whether to update the standard of care—and how to do so most efficiently—included:

- ◆ Could the new standard of care be combined safely with each research treatment currently being tested in the trial?
- ◆ Could the new standard of care be combined feasibly with each research treatment currently being tested in the trial?
- ◆ How would study processes need to change in response to the standard of care change being implemented—from study eligibility to data collection to safety data review?

The need for consensus added an extra layer of complexity to these decisions. Master protocols can only be successful with the buy-in of a diverse stakeholder group, so all potential changes had to be communicated to all stakeholders, including investigators, patient representatives, and, if the proposed change would increase the duration of ongoing comparisons, funders.

SOLUTION

With every change and resulting decision, the study team was able to reach a satisfactory decision by beginning with smaller, team-level conversations that eventually scaled to a broader organizational level, building consensus along the way and making multi-disciplinary decisions. Once the internal team weighed risks and benefits of a proposed adjustment, the discussion then went to a broader trial management group, involving different perspectives such as clinicians. Then external partners and stakeholders were also involved in the discussion.

The standard-of-care has often been updated to allow choice in order to be inclusive and representative. All patients receive long-term hormone therapy. Radiotherapy is now mandated for non-metastatic patients and encouraged for metastatic patients, unless there is a contradiction to radiotherapy, like certain co-morbid bowel conditions. Patients can also receive chemotherapy or novel hormone therapy (where available) but not both. Importantly, this choice is made by the investigators before randomization and this serves as a stratification factor at randomization.

OUTCOMES

Ongoing platform trials are more likely to face multiple standard of care changes than are traditional clinical trials because they are conducted over a longer time span. These standard of care changes may originate from within or outside the platform trial.

- ◆ The study team needs to demonstrate how the standard of care can feasibly be applied in clinical practice.
- ◆ The study team needs to consider how the ongoing questions being explored in the platform can be adapted to react to changes in the standard of care. Any alterations to the trial need to be made in a responsive way that is considerate of the questions already being explored.

Conducting an ongoing platform trial has enabled the STAMPEDE team to publish the results of seven Phase III trials, with further relevant results to follow. The use of an ongoing platform also resulted in the following positive outcomes:

- ◆ Fewer patients were needed for one platform trial than would have been needed for multiple separate trials.
- ◆ This trial design can be more cost effective than running separate trials.
- ◆ Results are found and shared sooner in an ongoing platform.

SUCCESS FACTORS

The study team has the following advice for others facing standard of care changes and considering how to implement these changes into a trial with a platform protocol:

- ◆ Always take an interdisciplinary approach to decision-making.
- ◆ Decision making is two-fold, as the study team will need to consider whether the standard of care change should be implemented in the trial, and how that implementation can feasibly be conducted. Decision making should include all the stakeholders that have been present for the planning and design of the master protocol, including:
 - Clinical experts who can weigh in on how the standard of care change will interact with investigational arms, as well as any safety concerns
 - Operational experts who can assess the feasibility of implementing a change, both within the central study team and on the site level
 - Statistical experts who can consider the changes' implications on the data across the life of the trial
 - Patient representatives who can provide input on the implications of making a change
 - Communications experts who can provide messaging about why the change is being implemented
- ◆ Ensure changes made to the study maximize potential benefits for its future participants while minimizing harm.
- ◆ Don't rush decisions and take time to weigh implications of all options.

- ◆ It may not always be the best option to implement the standard of care change, and in some cases, it should not be done.
 - For example, if a change is made too late in the recruitment stage for one of the comparison arms, implementing the standard of care change may render the results too difficult to interpret.
 - In another example, sometimes the new standard of care cannot be safely or feasibly combined with an ongoing test treatment.
- ◆ Focus on site training and make sure that all stakeholders are informed of any changes made to the study. Site input on proposed changes is important; for example, study teams need to make sure that sites have the resources they need to actually implement a standard of care change (e.g. do sites have access to the new standard of care?)